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*Brief Clinical Report*

# Hirschsprung Disease, Postaxial Polydactyly, and Atrial Septal Defect

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**We report on an infant girl with Hirschsprung disease, postaxial polydactyly, and atrial septal defect who was born to a consanguineous Iraqi couple. A similar condition of aganglionic megacolon, postaxial polydactyly, and ventricular septal defect with a presumed autosomal recessive (AR) inheritance was reported by Laurence in two sibs [Laurence et al.; J Med Genet 12: 334–338, 1975]. Am. J. Med. Genet. 68:74–75, 1997** © 1997 Wiley-Liss, Inc.

**KEY WORDS: congenital aganglionic megacolon; autosomal recessive inheritance**

## INTRODUCTION

We report on an infant girl with Hirschsprung disease (HSCH), postaxial polydactyly of the hands, and atrial septal defect (ASD). This condition was reported in two sibs by Laurence [1975]. The severity of congenital abnormalities led to death of one of the sibs. Malformations occur frequently in HSCH, however, this particular combination of abnormalities has not been described since Laurence's original report. The parental consanguinity in this case suggests that our patient represents a milder form of the same AR syndrome.

## CLINICAL REPORT

A girl was born at 41 weeks of gestation following an uncomplicated pregnancy and a spontaneous vaginal vertex delivery to a healthy G3 P2 Iraqi woman. Bilateral postaxial polydactyly was noted at birth. The infant was discharged on day 2 after the supernumerary digit was removed on the right side. On day 4 she presented with abdominal distention and decreased urine output. Abdominal radiograph showed distended bowel loops. The infant was admitted for investigations and management.

The parents, Arabs from Iraq, are first cousins, and have two older healthy daughters. There was no family history of HSCH, or congenital heart disease.

She was a vigorous, responsive infant in no apparent distress. Weight was 3.475 kg (50th–75th centile), length was 49 cm (50th centile), and head circumference (OFC) was 33.5 cm (3rd–10th centile). Facial appearance was normal. The second heart sound was fixed. There was a systolic II/VI murmur at the left sternal border. The abdomen was soft and distended with no organomegaly; the anus was patent, and external genitalia were normal. There was a well-formed triphalangeal supernumerary digit with a normal nail on the ulnar side of the left hand (Fig. 1), and a nubbin of tissue on the ulnar side of the right hand where the supernumerary digit had been removed.

Chest radiograph and 12-lead electrocardiogram were normal. Renal ultrasound results were normal. Radiographs of the hands showed no duplication or widening of the fifth metacarpals, and a well-formed triphalangeal supernumerary digit on the left. Radiographs of the feet were normal. Head ultrasound findings were normal. Karyotype was 46,XX. Rectal biopsy showed a complete absence of ganglion cells in the myenteric plexus. She underwent a one-stage Soave procedure (endorectal pull-through) for the correction of HSCH at day 17 of life with excellent result.

At age 1 year the child's growth, nutrition, and development were normal. There was no evidence of cardiac disease, nor of deafness.

## DISCUSSION

HSCH (aganglionic megacolon) is characterized by the absence of intramural ganglion cells along variable lengths of the myenteric and submucosal plexuses of the gastrointestinal tract. HSCH is genetically heterogeneous. Segregation of HSCH as an autosomal dominant (AD) trait has been reported in several large pedigrees [Reyna, 1994]. The recognition of a deletion of 10q(q11.2q21.2) associated with Hirschsprung disease

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Fig. 1. Left hand with postaxial polydactyly.

[Fewtrell et al., 1994] preceded the mapping of the gene for HSCH to the pericentromeric region of chromosome 10 [Angrist et al., 1993], and the discovery of the relationship of RET mutations in HSCH [Romeo et al., 1994; Edery et al., 1994]. The recent report of a missense mutation of the endothelin-B receptor gene in HSCH showed a dosage-sensitive mutation in an inbred Mennonite pedigree with AR inheritance [Puffenberger et al., 1994]. HSCH has also been described in trisomy 21 [Knox and Bensel, 1972], and Smith-Lemli-Opitz type II [Patterson et al., 1983]. HSCH also occurs in numerous other abnormalities of the neural crest: Ondine's curse [Haddad et al., 1978]; bilateral bicolored irides [Liang et al., 1983]; cutaneous piebaldism, bicolored irides, and congenital deafness [Goldberg 1966]; Waardenburg syndrome [Branski et al., 1979; Omenn and McKusick, 1979]; and microcephaly and iris coloboma [Hurst et al., 1988]. Recently, a mutation in the endothelin B gene was reported in a consanguineous family with Waardenburg syndrome and HSCH inherited recessively [Attie et al., 1995]. Several other constellations of congenital anomalies associated with HSCH are not easily explained by involvement of the neural crest: HSCH, unilateral renal agenesis, and sensorineural deafness [Santos et al., 1988]; hypoplastic nails and minor anomalies [Al-Gazali et al., 1988]; brachydactyly with inheritance pattern suggestive of X-linked recessive inheritance [Reynolds et al., 1983]; and two sibs with HSCH associated with ventricular septal defect, broad big toes, and ulnar polydactyly [Laurence et al., 1975].

Our patient with HSCH, postaxial polydactyly, and a clinical diagnosis of ASD is similar to the two sibs reported by Laurence [1975]. There was no evidence of renal disease or malformation, nor of hearing loss. Parental consanguinity in our patient supports an AR mode of inheritance. This is the third case of the AR syndrome reported by Laurence [1975], supporting the concept that the constellation of HSCH, polydactyly, and congenital heart defect represents a distinct AR malformation syndrome.

## REFERENCES


Al-Gazali LI, Donnai D, Mueller RF (1988): Hirschsprung disease, hypoplastic nails and minor dysmorphic features: A distinct autosomal recessive syndrome? J Med Genet 25:758–610.

Angrist M, Kauffman E, Slaugenhaupt SA, Matis TC, Puffenberger EG, Washington SS, Lipson A, Cass DT, Reyna T, Weeks DE, Sieber W, Chakravarti A (1993): A gene for Hirschsprung disease (megacolon) in the pericentromeric region of human chromosome 10. Nat Genet 4:351–356.

Attie T, Till M, Amiel J, Edery P, Pelet A, Munnich A, Lyonnet S (1995): Endothelin receptor B gene mutation in a consanguineous family with Waardenburg-Hirschsprung disease. Am J Hum Genet 57:A6.

Branski D, Dennis NR, Neale JM, Brook L (1979): Hirschsprung disease and Waardenburg syndrome. Pediatrics 63:803–805.

Edery P, Lyonnet S, Mulligan LM, Pelet A, Dow E, Abel L, Holder S, Nihoul-Fekete C, Ponder BAJ, Munnich A (1994): Mutations of the RET proto-oncogene in Hirschsprung disease. Nature 367: 378–380.

Fewtrell MS, Tam PKH, Thomson AH, Fitchett M, Currie J, Huson SM, Mulligan LM (1994): Hirschsprung disease associated with a deletion of chromosome 10 (q11.2q21.2): A further link with the neurocristopathies? J Med Genet 31:325–327.

Goldberg MF (1966): Waardenburg syndrome with fundus and other abnormalities. Arch Ophthalmol 40:797–810.

Haddad GG, Mazza NM, Defendini R, Blanc WA, Driscoll JM, Epstein MAF, Epstein RA, Mellins RB (1978): Congenital failure of automatic control of ventilation, gastrointestinal motility and heart rate. Medicine (Baltimore) 57:517–526.

Hurst JA, Markiewicz M, Kumar D, Brett EM (1988): Hirschsprung disease, microcephaly, and iris coloboma: A new syndrome of defective neuronal migration. J Med Genet 25:494–500.

Knox GE, Bensel RW (1972): Gastrointestinal malformations in Down syndrome. Minn Med 55:542–544.

Laurence KM, Prosser R, Rocker I, Pearson JF, Richards C (1975): Hirschsprung disease associated with congenital heart malformation, broad big toes, and ulnar polydactyly in sibs: A case for fetoscopy. J Med Genet 12:334–338.

Liang JC, Juarez CP, Goldberg MF (1983): Bilateral bicolored irides with Hirschsprung disease: A neural crest syndrome. Arch Ophthalmology 101:69–73.

Omenn GS, McKusick VA (1979): The association of Waardenburg syndrome and Hirschsprung megacolon. Am J Med Genet 3: 217–223.

Patterson K, Tooney KE, Chandra RS (1983): Hirschsprung disease in a 46, XY, phenotypic infant girl with Smith-Lemli-Opitz syndrome. J Pediatr 103:425–427.

Puffenberger EG, Hosoda K, Washington SS, Nakao K, deWit D, Yanagisawa Y, Chakravarti A (1994): A missense mutation of the endothelin-B receptor gene in multigenic Hirschsprung disease. Cell 79:1257–1266.

Reyna TM (1994): Familial Hirschsprung's disease: Study of a Texas cohort. Pediatrics 94:347–349.

Reynolds JF, Barber JC, Alford BA, Chandler JG, Kelly TE (1983): Familial Hirschsprung disease and type D brachydactyly: A report of four affected males in two generations. Pediatrics 71:246–249.

Romeo G, Ronchetto P, Luo Y, Barone V, Seri M, Ceccherini I, Pasini B, Bocciardi R, Lerone M, Kaarlainene H, Martuciello G (1994): Point mutation affecting the tyrosine kinase domain of the RET proto-oncogene in Hirschsprung's disease. Nature 367:377–378.

Santos H, Mateus J, Leal MJ (1988): Hirschsprung disease associated with polydactyly, unilateral renal agenesis, hypertelorism, and congenital deafness: A new autosomal recessive syndrome. J Med Genet 25:204–208.